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Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

HBVAXPRO

International non-proprietary name: HEPATITIS B VACCINE (RDNA)

Procedure No. EMEA/H/C/000373/P46/052

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Assessment

1.1. Introduction

This final report of a paediatric study P46 052 was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 of the European Parliament:

P46 052 is "an open-label, randomised, controlled, multicentre study of the immunogenicity and safety of a booster dose of two different hepatitis b vaccines [HBVAXPRO, 5 µg (modified process) versus Engerix-B, 10 µg) to explore the anamnestic immune response in healthy 4 to 7 year-old children previously vaccinated at about 3, 5 and 11 to 13 months of age with either HEXAVAC or INFANRIX-HEXA ".

2. STUDY DESIGN:

This study was designed to describe the Hepatitis B antibody responses after a booster dose of 2 different Hepatitis B vaccines licensed for children and adolescents from birth through 15 years of age: HBVaxPRO or ENGERIX-B 10 µg.

This study was open-label and conducted in 2 parts:

Part I

- 28 to 42 days of the study. All subjects participated to Part I of the study. At inclusion (Visit 1), within each hexavalent vaccine group (HEXAVAC or INFANRIX-HEXA Group), subjects were randomly assigned a booster dose of either HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg.

Previous Vaccination	Booster Dose	Group	
HEXAVAC® (3 doses)	HBVaxPRO® 5 µg (modified process)	Group 1	Group 1A
	ENGERIX-B® 10 µg		Group 1B
INFANRIX®-HEXA (3 doses)	HBVaxPRO® 5 µg (modified process)	Group 2	Group 2A
	ENGERIX-B® 10 µg		Group 2B

The planned sample size was 668 subjects, i.e. 167 subjects in each of the 4 subgroups.

Part II

- Children with an anti-HBs antibody titre <10 mIU/mL and being negative for anti-HBc antibody titre 1 month after the booster dose, as measured at Laboratorio Epatite, Università degli Studi di Milano, Italy, were proposed to continue to Part II of the study by receiving one or two extra-dose of a Hepatitis B vaccine, HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg.

- 3 months for children with an anti-HBs antibody titre <10 mIU/mL and negative for anti-HBc antibody titre 1 month after the booster dose and who accepted to be further vaccinated with one extra-dose of a Hepatitis B vaccine
- 7 months for children with an anti-HBs antibody titre <10 mIU/mL 1 month after the first extra-dose and who accepted to be further vaccinated with a second extra-dose of a Hepatitis B vaccine

Table 1: Vaccinations and Blood Sample Collections

	Part I		Part II			
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Timing for vaccination	Day 0		+ 2 months		+ 6 months	
Blood sample (BS)	BS1	BS2		BS3		BS4
Hepatitis B vaccine	Booster dose (a)		First extra-dose (b)		Second extra-dose (c)	

(a) HBVaxPRO® 5 µg (modified process) or ENGERIX-B® 10 µg
(b) proposed when anti-HBs antibody titre <10 mIU/mL and anti-HBc antibody titre test negative at BS 2 as measured at Laboratorio Epatite, Università degli Studi di Milano, Italy
(c) proposed when anti-HBs antibody titre <10 mIU/mL at BS 3 as measured at Laboratorio Epatite, Università degli Studi di Milano, Italy

3. STUDY OBJECTIVES

Primary objective:

- To describe in subjects vaccinated with 3 doses of HEXAVAC or 3 doses of INFANRIX-HEXA during the first 2 years of life the percentage of subjects with an anti-HBs antibody titre ≥ 10 mIU/mL (i.e. seroprotection rate) 1 month after a booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg.

Secondary objectives:

- To describe in subjects vaccinated with 3 doses of HEXAVAC or 3 doses of INFANRIX-HEXA during the first 2 years of life:
  - The percentage of subjects with an anti-HBs antibody titres >=5 mIU/mL (as stated in the Statistical Analysis Plan) and >=100 mIU/mL 1 month after a booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg
  - The anti-HBs antibody titres (GMT) 1 month after a booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg
  - The percentage of subjects with an anti-HBs antibody titres >=10 mIU/mL and >=100 mIU/mL and the GMT 1 month after a booster dose (4th dose of a Hepatitis B vaccine) of either HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg according to the pre-booster anti-HBs antibody titres

- In subjects that had received 1 or 2 extra-doses of a Hepatitis B vaccine, the individual anti-HBs antibody titres at 1 month after each extra-dose
- To describe the safety profile of HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg when administered as a booster dose (4th dose of a Hepatitis B vaccine).

4. DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Healthy subjects from 4 to 7 years of age; consent form signed by both parents or legal representative; no history of confirmed Hepatitis B or close contact with known carriers of Hepatitis B virus; prior receipt of 3 doses of HEXAVAC or INFANRIX-HEXA (2 doses during the first 6 months of life and the 3rd dose before the end of the second year of life) and no other Hepatitis B containing vaccine either alone or in combination; no known haematological, malignant or immunological disorder; no known sensitivity and/or allergy to any component of the study vaccine; no impairment of the immune system (including corticosteroids); no history of febrile illness in the past 3 days; no receipt of inactivated vaccine in the past 14 days or live vaccine in the past 28 days.

5. CRITERIA FOR EVALUATION

Primary endpoint:

The primary endpoint was the seroprotection rate defined as the percentage of subjects with an anti-HBs antibody titre ≥ 10 mIU/mL 1 month after the booster dose, as measured by the Ortho ECi assay at PPD Vaccines and Biologics LLC, USA, in all groups.

Secondary endpoints:

For immunogenicity in all groups:

Part I

- GMT, GMT ratio (GMTR) and percentage of subjects with an anti-HBs antibody titre >=5 mIU/mL (detectable antibody level, as stated in the Statistical Analysis Plan) and >=100 mIU/mL pre-booster and 1 month after the booster dose, and percentage of subjects with an anti-HBs antibody titre >= 10 mIU/mL pre-booster, as measured at PPD Vaccines and Biologics LLC, USA.

Part II

- Individual anti-HBs antibody titres 1 month after each extra-dose as measured at PPD Vaccines and Biologics LLC, USA
- Individual anti-HBs antibody titres 1 month after the booster dose and 1 month after the first extra-dose, as measured at Laboratorio Epatite, Università degli Studi di Milano, Italy

For safety in all groups:

Part I

- From Day 0 to Day 4, solicited adverse events
- From Day 0 to Day 14, unsolicited adverse events
- Serious adverse events

Part II

- Deaths and vaccine-related serious adverse events.

6. STATISTICAL METHODS

This study was descriptive. Data were summarised and no formal hypothesis was tested.

The immunogenicity analysis was performed on a Per Protocol Set (main analysis) and on a Full Analysis Set (supportive analysis) according to the results provided by PPD Vaccines and Biologics LLC, USA.

Descriptive statistics were provided for all 4 groups. In addition for immunogenicity, statistics were provided for the HEXAVAC Group (Groups 1A and 1B pooled) and the INFANRIX-HEXA Group (Groups 2A and 2B pooled); for safety, statistics were provided for the HBVaxPRO 5 µg (modified process) Group (Groups 1A and 2A pooled) and for the ENGERIX-B 10 µg Group (Groups 1B and 2B pooled).

Assessor's comments:

The current study is part of a post-suspension FUM originally requested to address the issue of long-term protection raised for HEXAVAC.

The design of this study was noted (in critical expert overview) to be agreed with EMA on December 2006.

7. RESULTS:

7.1. Disposition of Subjects

In total 410 subjects were included, including 62 in Groups 1A and 2A and 348 in 1B and 2B (Table 2).

Inclusions in Groups 1A and 2A were stopped at the time of HBVaxPRO 5 µg (modified process) expiry.

Table 2: Disposition of Subjects – Part I of the study

Previous vaccinations	Group 1 HEXAVAC®			Group 2 INFANRIX®-HEXA		
Booster	**Group 1A HBVaxPRO**	**Group 1B ENGERIX-B**	**All**	**Group 2A HBVaxPRO**	**Group 2B ENGERIX-B**	**All**
	n subjects (%)					
N included	34	167	201	28	181	209
N vaccinated	34 (100)	167 (100)	201 (100)	28 (100)	181 (100)	209 (100)
N completed	33 (97.1)	164 (98.2)	197 (98.0)	28 (100)	180 (99.4)	208 (99.5)
N withdrawn	1 (2.9)	3 (1.8)	4 (2.0)	0	1 (0.6)	1 (0.5)
Consent withdrawn	*1 (2.9)*	*0*	*1 (0.5)*	*0*	*1 (0.6)*	*1 (0.5)*
Lost to follow-up	*0*	*3 (1.8)*	*3 (1.5)*	*0*	*0*	*0*

HBVaxPRO stands for HBVaxPRO® 5 µg (modified process) - ENGERIX-B stands for ENGERIX-B® 10 µg

Number of subjects Analysed: The Full Analysis Set consisted of 401 subjects (97.8%): 195 subjects in Group 1 and 206 subjects in Group 2. The Per Protocol Set consisted of 391 subjects (95.4%): 193 subjects in Group 1 and 198 subjects in Group 2. The Safety Analysis Set consisted of 407 subjects (99.3%): 198 subjects in Group 1 and 209 subjects in Group 2.

Assessor's Comments:

The number of subjects receiving HBVaxPRO 5 µg (modified process) was less than initially planned (i.e. 167 subjects for each of 1A and 2A groups).

It was claimed to be due to the shortage of this vaccine. After HBVaxPRO 5 µg (modified process) expiry date, randomisation was stopped and all subjects received ENGERIX-B 10 µg.

The impact of using a reduced sample size on data analysis (especially immunogenicity comparison) might be limited, based on relatively small variation of the primary endpoint (narrowed post-challenge confidence intervals); however, it does preclude a better characterisation of the safety profile for this booster/challenge dose with HBVAXPRO in this age range of 4 – 7 years.

All recruited subjects got vaccinated. Endpoint analysis was performed with most of the recruited and vaccinated subjects. The drop-out rate among vaccinated subjects was very low.

7.2. Demography

Groups were comparable in terms of age at booster, weight, height and the time interval between the last hexavalent vaccine and the booster dose. Same results were observed in the Per Protocol Set and the Full Analysis Set.

7.3. Immunogenicity results

Part I

Primary immunogenicity analysis

- The post-booster rates of subjects with an anti-HBs antibody titre >=10 mIU/mL were 90.9% and 91.3% in the HEXAVAC groups (pooled for Group 1: 91.2%) and were 100% and 97.7% in the two INFANRIX-HEXA groups (pooled for Group 2: 98.0%) following HBVaxPRO and ENGERIX-B, respectively (see Table 3). Similar results were observed in the Full Analysis Set.

Secondary immunogenicity analyses

- The pre-booster rates of subjects with an anti-HBs antibody titre >=10 mIU/mL were 39.6% in the HEXAVAC Group and 81.3% in the INFANRIX-HEXA Group. The post-booster response rates were 92.2% in the HEXAVAC Group and 98.5% in the INFANRIX-HEXA Group at the level of 5 mIU/mL, and 82.9% in the HEXAVAC Group and 95.5% in the INFANRIX-HEXA Group at the level of 100 mIU/mL. The booster dose of HBVaxPRO or ENGERIX-B provided comparable response rates within each HEXAVAC and INFANRIX-HEXA Group (see Table 3).

Similar results were observed in the Full Analysis Set.

Table 3: Anti-HBs Response Rates – Per Protocol Set

Previous vaccinations		Group 1 HEXAVAC®			Group 2 INFANRIX®-HEXA		
Booster		**Group 1A HBVaxPRO (N=33)**	**Group 1B ENGERIX-B (N=160)**	**All (N=193)**	**Group 2A HBVaxPRO (N=27)**	**Group 2B ENGERIX-B (N=171)**	**All (N=198)**
		n subjects **(%)** [95% CI]					
anti-HBs >=5 mIU/mL	**Pre-booster**	21 **(63.6)** [45.1; 79.6]	71 **(44.7)** [36.8; 52.7]	92 **(47.9)** [40.7; 55.2]	21 **(77.8)** [57.7; 91.4]	145 **(84.8)** [78.5; 89.8]	166 **(83.8)** [78.0; 88.7]
	Post-booster	32 **(97.0)** [84.2; 99.9]	146 **(91.3)** [85.8; 95.1]	178 **(92.2)** [87.5; 95.6]	27 **(100)** [87.2; 100]	168 **(98.2)** [95.0; 99.6]	195 **(98.5)** [95.6; 99.7]
anti-HBs >=10 mIU/mL	**Pre-booster**	19 **(57.6)** [39.2; 74.5]	57 **(35.8)** [28.4; 43.8]	76 **(39.6)** [32.6; 46.9]	21 **(77.8)** [57.7; 91.4]	140 **(81.9)** [75.3; 87.3]	161 **(81.3)** [75.2; 86.5]
	Post-booster	30 **(90.9)** [75.7; 98.1]	146 **(91.3)** [85.8; 95.1]	176 **(91.2)** [86.3; 94.8]	27 **(100)** [87.2; 100]	167 **(97.7)** [94.1; 99.4]	194 **(98.0)** [94.9; 99.4]
anti-HBs >=100 mIU/mL	**Pre-booster**	3 **(9.1)** [1.9; 24.3]	9 **(5.7)** [2.6; 10.5]	12 **(6.3)** [3.3; 10.7]	11 **(40.7)** [22.4; 61.2]	74 **(43.3)** [35.7; 51.1]	85 **(42.9)** [35.9; 50.1]
	Post-booster	30 **(90.9)** [75.7; 98.1]	130 **(81.3)** [74.3; 87.0]	160 **(82.9)** [76.8; 87.9]	26 **(96.3)** [81.0; 99.9]	163 **(95.3)** [91.0; 98.0]	189 **(95.5)** [91.5; 97.9]

HBVaxPRO stands for HBVaxPRO® 5 µg (modified process) - ENGERIX-B stands for ENGERIX-B® 10 µg

The pre-booster GMTs were 9 mIU/mL in the HEXAVAC Group and 59 mIU/mL in the INFANRIX-HEXA Group. The post-booster GMTs ranged from 1255 to 878 mIU/mL in the two HEXAVAC groups (pooled for Group 1: 934 mIU/mL), and from 6564 to 7420 mIU/mL in the two INFANRIX-HEXA groups (pooled

for Group 2: 7297 mIU/mL) following HBVaxPRO and ENGERIX-B, respectively. The GMTRs ranged from 100 to 111 in the two HEXAVAC groups and from 122 to 131 in the two INFANRIX-HEXA groups. The booster dose of HBVaxPRO or ENGERIX-B provided comparable GMTs and GMTRs within each HEXAVAC and INFANRIX-HEXA Group (see Table 4). Similar results were observed in the Full Analysis Set.

Assessor's comments:

Group 1A but not Group 2A contained a slightly higher percentage of subjects with pre-booster anti-HBs antibodies >=5 mIU/ml, >=10 mIU/ml, >=100 mIU/ml, as compared to its own control group. This finding doesn't appear to affect the conclusion that HBVAXPRO is comparable to Engerix-B with respect to immunogenicity in this study.

However, the overall pre-booster data in Table 3 suggest that after primary vaccination series, HEXAVAC achieved significantly lower anti-HBs response than INFANRIX-HEXA (47.9% vs 83.8% at > = 5 mIU/ml; 39.6% vs 81.3% at > = 10 mIU/ml; 6.3% vs 42.9% at > = 100 mIU/ml. This finding may suggest that children previously vaccinated with HEXAVAC may have increased risk of hepatitis B virus infection than children vaccinated with INFANRIX-HEXA.

Table 4: Anti-HBs GMT and GMTR – Per Protocol Set

Previous vaccinations		Group 1 HEXAVAC®			Group 2 INFANRIX®-HEXA		
Booster		Group 1A HBVaxPRO (N=33)	Group 1B ENGERIX-B (N=160)	All (N=193)	Group 2A HBVaxPRO (N=27)	Group 2B ENGERIX-B (N=171)	All (N=198)
		[95% CI]					
GMT mIU/mL	Pre-booster	**13** [7; 22]	**8** [6; 10]	**9** [7; 11]	**50** [23; 109]	**61** [45; 82]	**59** [45; 78]
	Post-booster	**1255** [554; 2846]	**878** [581; 1327]	**934** [647; 1348]	**6564** [2917; 14772]	**7420** [5227; 10531]	**7297** [5300; 10045]
GMTR		**100** [57; 175]	**111** [80; 154]	**109** [82; 145]	**131** [83; 205]	**122** [96; 155]	**123** [99; 153]

HBVaxPRO stands for HBVaxPRO® 5 µg (modified process) - ENGERIX-B stands for ENGERIX-B® 10 µg
GMT: Geometric mean of anti-HBs antibody titres
GMTR: Geometric mean of individual post-/pre-booster anti-HBs antibody titres

A *post-hoc* analysis was performed on the subsets of subjects with a pre-booster anti-HBs titre <10 and >=10 mIU/mL. Subjects with a pre-booster anti-HBs titre <10 mIU/mL had post-booster GMTs at 284 mIU/mL in the HEXAVAC Group and 339 mIU/mL in INFANRIX-HEXA Group, and GMTRs at 97 in the HEXAVAC Group and 118 in the INFANRIX-HEXA Group. The rates of subjects with an anti-HBs >=10 mIU/mL were 85.3% in the HEXAVAC Group and 91.9% in the INFANRIX-HEXA Group. All of the subjects with a pre-booster anti-HBs titre >=10 mIU/mL had a post-booster titre >=100 mIU/mL, except one subject in the INFANRIX-HEXA Group (see Table 5).

Table 5: Post-booster anti-HBs Response Rates, GMT and GMTR in Subjects <10 mIU/mL and >=10 mIU/mL Pre-booster – Per Protocol Set – *Post-hoc* analysis

Previous vaccinations		Group 1 HEXAVAC®		Group 2 INFANRIX®-HEXA	
Booster		**HBVaxPRO or ENGERIX-B (N=193)** (a)		**HBVaxPRO or ENGERIX-B (N=198)**	
		<10 mIU/mL N=116	**>=10 mIU/mL N=76**	**<10 mIU/mL N=37**	**>=10 mIU/mL N=161**
anti-HBs >=10 mIU/mL n subjects **(%)** [95% CI]		99 **(85.3)** [77.6; 91.2]	76 **(100)** [95.3; 100]	34 **(91.9)** [78.1; 98.3]	160 **(99.4)** [96.6; 100]
anti-HBs >=100 mIU/mL n subjects **(%)** [95% CI]		83 **(71.6)** [62.4; 79.5]	76 **(100)** [95.3; 100]	29 **(78.4)** [61.8; 90.2]	160 **(99.4)** [96.6; 100]
GMT mIU/mL [95% CI]	**Pre-booster**	**3** [3; 3]	**45** [33; 60]	**3** [3; 3]	**119** [94; 149]
	Post-booster	**284** [180; 449]	**5764** [4122; 8059]	**339** [172; 667]	**14776** [11391; 19168]
GMTR [95% CI]		**97** [63; 151]	**129** [96; 174]	**118** [61; 229]	**125** [100; 155]

HBVaxPRO stands for HBVaxPRO® 5 µg (modified process) - ENGERIX-B stands for ENGERIX-B® 10 µg
(a) One pre-booster missing data

Assessor's comments:

Descriptive statistics were provided for all 4 subgroups and in addition for the HEXAVAC Group and for the INFANRIX-HEXA Group (by pooling infants having been boosted with HBVaxPRO 5 µg modified process or ENGERIX-B 10 µg):

- The post-booster rates of subjects with anti-HBs >=10 mIU/mL ranged from 90.9% to 91.3% for the two HEXAVAC groups
- The post-booster GMTs ranged from 878 to 1255 mIU/mL for the two HEXAVAC groups
- The post-booster rates of subjects with anti-HBs >=10 mIU/mL ranged from 97.7% to 100% for the two INFANRIX-HEXA groups
- The post-booster GMTs ranged from 6564 to 7420 mIU/mL for the two INFANRIX-HEXA groups
- The GMTRs ranged from 100 to 131 for the two HEXAVAC and the two INFANRIX-HEXA groups
- In the subset of subjects with a pre-booster anti-HBs titre <10 mIU/mL, the post-booster rates of subjects with anti-HBs titre >=10 mIU/mL were 85.3% and 91.9%, the post-booster GMTs were 284 and 339 mIU/mL and the GMTRs were 97 and 118 in the HEXAVAC Group and the INFANRIX-HEXA Group, respectively
- All of the subjects with a pre-booster anti-HBs titre >=10 mIU/mL had a post-booster titre >=100 mIU/mL, except one subject in the INFANRIX-HEXA Group
- All of the subjects who received one or two extra-dose(s) of hepatitis b vaccine achieved an anti-HBs antibody titer >= 10 mIU/ml, except two subjects in the HEXAVAC group
- In each HEXAVAC and INFANRIX-HEXA Group, the booster dose of HBVaxPRO 5 µg (modified process) or ENGERIX-B 10 µg stimulated comparable immune responses.

Part II

- Fifteen (15) subjects continued in Part II of the study, 14 in the HEXAVAC Group and 1 in the INFANRIX-HEXA Group, and received one extra-dose of a Hepatitis B vaccine. One subject, in Group 1A, received HBVaxPRO and the other subjects received ENGERIX-B. Three out of the 15 subjects, all in the HEXAVAC Group, received a second extra-dose of ENGERIX-B.
- All of the subjects who received one or two extra-dose(s) of Hepatitis B vaccine achieved an anti-HBs antibody titre >=10 mIU/mL, except two subjects in the HEXAVAC Group: one subject had an anti-HBs antibody titre at 6.5 mIU/mL following the first extra-dose of ENGERIX-B 10 µg and did not receive a second extra-dose (as it was tested at 10.5 mIU/mL by the Italian Lab following the first extra-dose), and one subject remained seronegative (<5 mIU/mL) after the second extra-dose of ENGERIX-B 10 µg

Assessor's comments:

The finding of 14 out of 15 subjects who were in HEXAVAC groups and did not achieve a protective titer of 10 mIU/ml after the booster/challenge dose, either with HBVAXPRO or Engerix-B, is interesting, and is consist with the finding that vaccination with HEXAVAC achieved significantly lower anti-HBs responses than INFANRIX-HEXA, as suggested by overall pre-booster data presented in Table 3 and Table 4.

From Part I: The pre-booster rates of subjects with an anti-HBs antibody titre >=10 mIU/mL were 39.6% in the HEXAVAC Group versus 81.3% in the INFANRIX-HEXA Group. The pre-booster GMTs were 9 mIU/mL in the HEXAVAC Group versus 59 mIU/mL in the INFANRIX-HEXA Group.

7.4. Safety results

Part I (see Table 6)

From Day 0 to Day 14, 24.2% of subjects reported injection-site adverse reactions and 24.2% systemic adverse events in the HBVaxPRO 5 µg (modified process) Group, and 31.6% and 19.4% in the ENGERIX-B 10 µg Group, respectively.

All injection-site adverse reactions occurred between Day 0 and Day 4 and all were solicited (namely injection-site erythema, pain and swelling), except 3 in the ENGERIX-B 10 µg Group (injection-site haemorrhage, irritation and pruritus).

In the ENGERIX-B Group, children previously vaccinated with INFANRIX-HEXA presented more solicited injection-site adverse reactions (total: 37.6%, erythema: 8.8%, pain: 32.6%, swelling: 7.2%) than those previously vaccinated with HEXAVAC (total: 24.4%, erythema: 1.2%, pain: 23.2%, swelling: 1.8%), with a non-overlap of the confidence intervals for injection-site erythema only. The sample sizes of the two HBVaxPRO groups were too small (34 and 28 subjects, respectively) to allow any meaningful safety analysis. In both groups, most injection-site adverse reactions were of mild intensity or with a size <2.5 cm and lasted 3 days or less.

Few subjects reported solicited systemic adverse events (i.e. pyrexia) between Day 0 and Day 4: 6.5% (vaccine-related: 1 subject [1.6%]) in the HBVaxPRO 5 µg (modified process) Group and 3.2%

(vaccine-related: 6 subjects [1.7%]) in the ENGERIX-B 10 µg Group. Similarly, few subjects reported unsolicited systemic adverse events between Day 0 and Day 14: 21.0% (vaccine-related: 1 subject [1.6%]) in the HBVaxPRO 5 µg (modified process) Group and 17.4% (vaccine-related: 8 subjects [2.3%]) in the ENGERIX-B 10 µg Group.

Only one unsolicited systemic adverse event was reported with an incidence >=5% in at least one group: pyrexia in the ENGERIX-B Group between Day 5 and Day 14 (6.1%, vaccine-related: 0.3%).

In both groups, body temperature was mostly >=38.0°C and <=39.0°C and lasted usually 3 days or less for both solicited and unsolicited pyrexia. Unsolicited vaccine-related systemic adverse event were mostly of mild intensity and lasted mainly 3 days or less in both groups.

From Day 0 to Visit 2, 5 serious adverse events were reported by 4 subjects, all from the ENGERIX-B 10 µg Group (1.2%): chest pain, infectious mononucleosis, parotitis associated with tracheobronchitis mycoplasmal and diabetes mellitus inadequate control. None of them were assessed by the investigator to be related to ENGERIX-B 10 µg and all resolved in 1 to 7 days.

No subjects were withdrawn from the study due to an adverse event.

Part II

No deaths and vaccine-related serious adverse events were reported.

Table 6: Global Summary of Safety – Part I of the study - Safety Analysis Set

Booster	Group A HBVaxPRO® 5 µg (modified process)			Group B ENGERIX-B® 10 µg		
Previous vaccinations	**Group 1A HEXAVAC (N=34)**	**Group 2A INFANRIX-HEXA (N=28)**	**All (N=62)**	**Group 1B HEXAVAC (N=164)**	**Group 2B INFANRIX-HEXA (N=181)**	**All (N=345)**
	n subjects **(%)** [95% CI]					
ISR or systemic AE in Days 0-14	16 **(47.1)** [29.8; 64.9]	10 **(35.7)** [18.6; 55.9]	26 **(41.9)** [29.5; 55.2]	63 **(38.4)** [30.9; 46.3]	83 **(45.9)** [38.4; 53.4]	146 **(42.3)** [37.0; 47.7
ISR in Days 0-14	7 **(20.6)** [8.7; 37.9]	8 **(28.6)** [13.2; 48.7]	15 **(24.2)** [14.2; 36.7]	40 **(24.4)** [18.0; 31.7]	69 **(38.1)** [31.0; 45.6]	109 **(31.6)** [26.7; 36.8
Solicited ISR in Days 0-4	7 **(20.6)** [8.7; 37.9]	8 **(28.6)** [13.2; 48.7]	15 **(24.2)** [14.2; 36.7]	40 **(24.4)** [18.0; 31.7]	68 **(37.6)** [30.5; 45.1]	108 **(31.3)** [26.4; 36.5
Injection-site erythema	**0** [0; 10.3]	1 **(3.6)** [0.1; 18.3]	1 **(1.6)** [0; 8.7]	2 **(1.2)** [0.1; 4.3]	16 **(8.8)** [5.1; 14.0]	18 **(5.2)** [3.1; 8.1]
Injection-site pain	7 **(20.6)** [8.7; 37.9]	7 **(25.0)** [10.7; 44.9]	14 **(22.6)** [12.9; 35.0]	38 **(23.2)** [16.9; 30.4]	59 **(32.6)** [25.8; 39.9]	97 **(28.1)** [23.4; 33.2
Injection-site swelling	**0** [0; 10.3]	2 **(7.1)** [0.9; 23.5]	2 **(3.2)** [0.4; 11.2]	3 **(1.8)** [0.4; 5.3]	13 **(7.2)** [3.9; 12.0]	16 **(4.6)** [2.7; 7.4]
Unsolicited ISR in Days 0-14	**0** [0; 10.3]	**0** [0; 12.3]	**0** [0; 5.8]	**0** [0; 2.2]	3 **(1.7)** [0.3; 4.8]	3 **(0.9)** [0.2; 2.5]
Systemic AE in Days 0-14	10 **(29.4)** [15.1; 47.5]	5 **(17.9)** [6.1; 36.9]	15 **(24.2)** [14.2; 36.7]	30 **(18.3)** [12.7; 25.1]	37 **(20.4)** [14.8; 27.1]	67 **(19.4)** [15.4; 24.0
Solicited systemic AE in Days 0-4: pyrexia	3 **(8.8)** [1.9; 23.7]	1 **(3.6)** [0.1; 18.3]	4 **(6.5)** [1.8; 15.7]	6 **(3.7)** [1.4; 7.8]	5 **(2.8)** [0.9; 6.3]	11 **(3.2)** [1.6; 5.6]
Vaccine-related pyrexia	**0** [0; 10.3]	1 **(3.6)** [0.1; 18.3]	1 **(1.6)** [0; 8.7]	3 **(1.8)** [0.4; 5.3]	3 **(1.7)** [0.3; 4.8]	6 **(1.7)** [0.6; 3.7]
Unsolicited systemic AE in Days 0-14	8 **(23.5)** [10.7; 41.2]	5 **(17.9)** [6.1; 36.9]	13 **(21.0)** [11.7; 33.2]	26 **(15.9)** [10.6; 22.4]	34 **(18.8)** [13.4; 25.2]	60 **(17.4)** [13.5; 21.8
Vaccine-related unsolicited systemic AE	1 **(2.9)** [0.1; 15.3]	**0** [0; 12.3]	1 **(1.6)** [0; 8.7]	2 **(1.2)** [0.1; 4.3]	6 **(3.3)** [1.2; 7.1]	8 **(2.3)** [1.0; 4.5]
SAE from Day 0 to Visit 2	**0** [0; 10.3]	**0** [0; 12.3]	**0** [0; 5.8]	3 **(1.8)** [0.4; 5.3]	1 **(0.6)** [0; 3.0]	4 **(1.2)** [0.3; 2.9]
Vaccine-related SAE	**0** [0; 10.3]	**0** [0; 12.3]	**0** [0; 5.8]	**0** [0; 2.2]	**0** [0; 2.0]	**0** [0; 1.1]
Withdrawal for AE	**0** [0; 10.3]	**0** [0; 12.3]	**0** [0; 5.8]	**0** [0; 2.2]	**0** [0; 2.0]	**0** [0; 1.1]

n subjects (%): number (percentage) of subjects presenting at least once the considered event
ISR: Injection-site adverse reaction
AE: Adverse event
SAE: Serious adverse event

Assessor's comments:

Descriptive statistics were provided for all 4 subgroups and in addition for the HBVaxPRO 5 µg (modified process) Group and for the ENGERIX-B 10 µg Group (by pooling infants having been previously vaccinated with HEXAVAC or INFANRIX-HEXA). The safety analysis set comprised of 62 subjects who received HBVaxPRO 5 µg (modified process) Group and 345 subjects who received ENGERIX-B 10 µg.

Overall, the booster doses of HBVaxPRO 5 µg (modified process) and ENGERIX-B 10 µg appeared to be well tolerated. However, this conclusion is rather preliminary, because the sample sizes of the two HBVaxPRO groups were too small (34 and 28 subjects, respectively) to allow any meaningful safety analysis.

8. Rapporteur's Overall Conclusion And further action if required

PAC No.: P46 052

8.1. Overall Conclusion / Outstanding Issue:

The study was designed for descriptive analysis only and the protocol was noted (in short critical expert overview) to be agreed upon by the EMA in December 2006.

One significant finding from this study report is the significantly lower pre-booster immune response induced by HEXAVAC compared with that induced by the INFANRIX-HEXA (47.9% vs 83.8% at > = 5 mIU/ml; 39.6% vs 81.3% at > = 10 mIU/ml; 6.3% vs 42.9% at > = 100 mIU/ml). Furthermore, after post-booster dose, 14 out of 15 subjects in the HEXAVAC groups did not achieve a protective titer of 10 mIU/ml. This finding suggests that children previously vaccinated with HEXAVAC may have increased risk of hepatitis B virus infection than children vaccinated with INFANRIX-HEXA.

The other significant finding of this study report is the less than planned number of subjects received HBVAXPRO booster/challenge dose: only 62 subjects in total (34 in 1A and 28 in 2A groups) received HBVAXPRO/modified process, much less than originally planned (167 in 1A and 167 in 2A). This was explained by the MAH to be due to the shortage of HBVAXPRO/modified process (the lot of HBVaxPRO 5 µg (modified process) used at the time the study started (27 October 2008) expired on 14 March 2009 and at that time, due to equipment issues, the manufacture of a new lot was not possible in a reasonable timing).

Nonetheless, all recruited subjects were vaccinated and most were evaluated for primary and secondary endpoint analyses. The drop-out rate among vaccinated subjects was very low.

Importantly, pre-specified primary and secondary immunogenicity analyses consistently revealed that HBVaxPRO 5 µg (modified process) and ENGERIX-B 10 µg induced comparable anti-HBs anamnestic immune responses (endpoints: SPR of 10 mIU/ml, 100 mIU/ml, GMTs, GMTRs), either in HEXAVAC group or in INFANRIX-HEXA group, although children of two groups showed some degree of differences in pre-booster immunity. The post-booster responses showed relatively small variation in comparative groups (1A vs. 1B; 2A vs. 2B). The Assessor considers that these data from a total of 62 subjects in 1A and 2A may still provide relevant insight into comparability (immunogenicity) of HBVAXPRO and Engerix-B – which is the primary objective of the study, despite the fact of its limited size of 62 subjects.

Safety and reactogenicity of the challenge or booster dose of HBVAXPRO and Engerix-B in this study was among the secondary objectives. The reduced sample size of 62 children in total (34 in 1A and 28 in 2A groups) were too small to draw relevant conclusion.

In conclusion, the submission of this final study report, the descriptive nature of this study, together with the pre-defined primary analysis of the study and some relevant information provided on comparability of immunogenicity between HBVAXPRO and Engerix-B, may allow the assessor to temporarily consider this FUM as fulfilled. However, the firm conclusion on comparability of HBVAXPRO and Engerix-B is not well supported by the pre-booster data associated with primary vaccinations with HEXAVAC and INFANRIX-HEXA. In other words, HEXAVAC may be inferior to INFANRIX-HEXA in terms

of anti-HBs antibody persistence (lower percentages of subjects at > = 5 mIU/ml, > = 10 mIU/ml, > = 100 mIU/ml at pre-booster) and boostability (14 out of 15 subjects who did not achieve a anti-HBs titer of 10 mIU/ml were from the HEXAVAC group). In addition, reduction of the sample size in HBVAXPRO subgroups represented an obvious limitation of this study. This inconsistency of immunogenicity finding and limitation may need to be discussed in the context of the HBVAXPRO renewal process.

☒ PAC is considered completely fulfilled, that is, no request for further studies using a larger sample size at the time of this assessment. – However, the inconsistent finding of immunogenicity (HBVAXPRO comparable to Engerix-B versus HEXAVAC inferior to INFANRIX-HEXA) and the obvious limitation of small sample size of HBVAXPRO groups in the present study may be discussed in the context of the HBVAXPRO renewal process.